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Minocycline Augmentation of Pharmacotherapy in Obsessive-Compulsive Disorder: An Open-Label Trial

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Abstract

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To the editor

Most obsessive-compulsive disorder (OCD) patients treated with serotonin reuptake inhibitors (SRIs) show only partial reduction of symptoms.[1] Data suggest that OCD may be caused in part by glutamatergic dysfunction in orbito-frontal/basal ganglia brain circuits.[2, 3] and prior trials of glutamate modulators (e.g., riluzole, memantine) given as augmentation to SRIs suggest anywhere from 30% to 54% of OCD patients respond.[4–8]

We conducted a 12-week, prospective, open-label study to assess whether SRI augmentation with minocycline, a tetracycline derivative with putative glutamate modulating activity (i.e., enhancing glial glutamate transport)[9] in addition to its antibiotic properties, would improve OCD symptoms.

Advantages of minocycline include low cost (riluzole is expensive) and FDA approval in adults and children >12 years (memantine is only FDA approved in adults). Minocycline is the most widely prescribed antibiotic for chronic acne because its antibiotic resistance is lower than that of other tetracyclines and antimicrobials.[10] It has excellent side effect

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profile, even chronically: one study[11] showed minocycline taken for 2 years is well-tolerated, with no serious adverse effects.

Methods

Adult outpatients (N=9) aged 18 to 65 years who met *DSM-IV* criteria for OCD and had a Yale-Brown Obsessive-Compulsive Scale (Y-BOCS)[12] score of ≥16 despite a therapeutic SRI dose were recruited from the community between July 2008 and July 2009 and gave informed consent after the study procedures were fully explained. Institutional review board approval was obtained for the study. Subjects' SRI dose was stable for at least 12 weeks (and concomitant psychotropic medications for at least 4 weeks) prior to study entry. Subjects were excluded for current cognitive behavioral therapy, comorbid psychiatric or medical conditions that made participation unsafe, or use of medications that reduced the bioavailability of minocycline. Patients were assessed by an independent rater who administered the YBOCS (primary outcome measure), Hamilton Depression Inventory (HDRS, 17-item)[13], and Hamilton Anxiety Inventory (HARS)[14] every 2 weeks. Response was defined as at least a 30% reduction on the YBOCS.[15]

Subjects received minocycline at 50 mg bid for 3 days to ensure no allergic reaction, then at the FDA-approved adult dosing of 100 mg bid for 12 weeks in addition to their SRI. This dosing is expected to produce minocycline brain concentrations in the range that antagonize glutamate effects on neurons.[16, 17] All subjects completed the study, supporting the fact that minocycline was well tolerated. Outcome was analyzed using mixed-effects regression to model symptoms as a function of time.[18]

Results

Patient clinical characteristics are shown in Table 1.[19] OCD severity was moderate: mean (SD) YBOCS score at baseline was 28.2 (3.9), illness duration was 18.2 (10.4) years. Subjects were treatment-resistant: the mean number of prior SRI trials was 2.8 (1.6); 56% (5/9) had failed at least 1 adequate trial of antipsychotic augmentation, and 56% had failed an adequate trial of cognitive behavioral therapy. They had a range of OCD symptoms; one subject had hoarding as the primary symptom domain.

As a group, patients showed no significant differences in YBOCS, HDRS, or HARS rate of improvement over time (mixed effects regression: Y-BOCS, $z = -1.14$, $p = .25$; HAM-D, $z = .60$, $p = .55$; HAM-A, $z = .12$, $p = .90$). However, 2 of 9 patients (22%) met and exceeded treatment response criteria (40% and 46% Y-BOCS reduction). Both of these patients reported early onset of their OCD symptoms. One had primary hoarding, and 1 no longer met criteria for OCD at study end. Both chose to continue minocycline after study end.

These data suggest that minocycline augmentation of SRI pharmacotherapy may not improve OCD symptoms in all adult OCD patients, but may improve symptoms in those with early-onset OCD and those with primary hoarding. The robust response of 2 of 9 patients in this study coupled with the response of 2 other subjects (aged 16 and 17 years) with early-onset OCD in an identical parallel study of minocycline in adolescents (M.R., unpublished data, 2008) suggests that minocycline warrants further study. Early-onset OCD differs from later onset OCD in phenomenology, genetic risk, and SRI response.[20] Future studies should target early-onset OCD as well as focus on minocycline's mechanism of action.[21]

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Table 1

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of nine OCD patients treated with minocycline in addition to SRI/SNRI. Symptom dimensions were based inical severity for each subject: Cont (contamination obsessions and cleaning compulsions); Forbid Tht, ual, religious, and somatic obsessions and checking compulsions); Hrd (hoarding and saving obsessions and ns and repeating, ordering, and counting compulsions). AA, African American; C, Caucasian; Dysth, iety disorder; GF, grandfather; HAM-A, Hamilton Anxiety Rating Scale; HAM-D, Hamilton Depression ajor depressive disorder; OCD, obsessive-compulsive disorder; p, paternal; S, sister; SRI, serotonin inephrine reuptake inhibitor; Soc Phobia, social phobia; Speci Phobia, Specific Phobia; Substance Ab, essive-Compulsive Scale.

omain	Comorbid Diagnoses	Psychiatric Family History	Prior SRI Trials	Previous Anti-psychotic / or CBT	Current SRI / SNRI Daily Dose	Concommittant Psych Meds	Pre/Post YBOCS Score	Pre/Post HAM-D Score	Pre/Post HAM-A Score
	MDD	None	4	No/Yes	Fluoxetine 80mg	None	24/30	7/0	8/0
try	None	GAD (mother)	6	Yes/Yes	Duloxetine 60mg	None	29/28	0/3	0/3
orbid	MDD Soc Phobia	OCD (father, p uncle, p GF) Substance Ab (S)	2	No/No	Escitalopram 40mg	Zolpidem Clonazepam	29/26	12/10	9/7
Tht	MDD	None	4	Yes/No	Fluvoxamine 150mg	None	34/35	27/28	33/42
Tht,	MDD	OCD (daughter)	2	Yes/No	Fluoxetine 80mg	Lisdexamfetam ine dimesylate	29/25	8/14	12/18
orbid	MDD	OCD (father)	2	Yes/Yes	Fluvoxamine 300mg	None	29/29	0/3	0/2
rbid	Soc Phobia, GAD	Substance Ab (m cousin)	1	No/Yes	Sertraline 100mg	None	23/22	8/10	7/7
	MDD, Dysth Speci Phobia	Bipolar (mother, brother)	2	Yes/No	Fluoxetine 80mg	Buproprion Desvenlafaxine	33/20[a]	16/5	14/5
Tht,	None	Bipolar (father, m uncle, p aunt, p GF)	2	No/Yes	Fluoxetine 80mg	Clonzaepam Lisdexamfetam ine dimesylate	24/13 [a]	3/1	1/2

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